Remarks

The Office action mailed April 28, 2004, has been carefully reviewed. Claims 6, 13, 32 and 58 have been amended to provide correct antecedent basis. Claim 16 has been amended for purposes of clarification. New claims 95-102 have been added. Support for claims 95-97 is found in the specification, for example, at page 4, lines 13-21. Support for claims 98-100 is found in the specification, for example, at page 5, lines 6-9. Support for claims 101 and 102 is found in the specification, for example, at page 17, lines 15-19. Claims 64 and 65 have now been canceled. Entry of these amendments is respectfully requested. The pending rejections are traversed for the reasons explained below.

35 U.S.C. §112, second paragraph, rejections

Claims 13, 22, 32-42, 58, 64 and 65 have been rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness.

Claims 13 and 58 have been amended to provide proper antecedent basis.

Claim 22 has been amended to delete "about."

The phrase "the result of screening multiple tissue specimens" in line 8 of claim 32 finds proper antecedent basis in the phrase "screening multiple genes" in line 3 of claim 32. Thus, the rejection of claims 32-42 should be withdrawn.

Claims 64 and 65 have been canceled.

35 U.S.C. §102 rejections

Lampkin et al.

Claims 1, 2, 4, 6, 7, 13, 15 and 88 have been rejected under 35 U.S.C. §102(b) over Lampkin et al. A close review of Lampkin et al. reveals that this article does not disclose "comparing the results of the biological analysis in corresponding assigned locations of different substantial copies to determine if there are correlations between the results of the biological analysis at each assigned location" as recited in independent claim 1 (independent claim 88 contains a similar phrase). Lampkin et al. mentions that the tissue blocks prepared therein may be used for determining optimal fixation for various immunoreagents or for characterizing immunoreagent specificity and sensitivity (see page 122, second column). The Office action on

page 4 characterizes Lampkin et al. as describing "performing analysis of each copy and comparing the results of the analysis." However, Lampkin et al. contains no description of how the immunoreagent analyses are performed, much less a specific description of comparing and correlating results from "corresponding assigned locations of different substantial copies" as recited in claims 1 and 88. In this regard, it is important to recognize that claims 1 and 88 contemplate more than just comparing the results of the analysis as stated in the Office action on page 4. Claims 1 and 88 also include correlating the results from corresponding assigned different substantial copies. Absent a disclosure of such a correlation, Lampkin et al. must fail as an anticipatory reference.

In addition, dependent claim 6 recites a step of placing an elongated donor specimen in an elongated receptacle of the recipient block. Contrary to the assertion on page 4 of the Office action, such placement step does not occur in the method of Lampkin et al. Instead, "individually prepared sample cores are manually aligned in a rectangular grid-like arrangement in a base mold, covered with a plastic cassette, and embedded within paraffin to produce the finished multiple sample block" (page 122, first column). Thus, the samples cores are embedded within paraffin rather than placed in an elongated receptacle already formed in the paraffin block as recited in claim 6.

Kraaz et al.

Claims 1-7, 9-15, 49 and 88 have been rejected under 35 U.S.C. §102(b) over Kraaz et al. A review of Kraaz et al. reveals that it suffers from the same deficiencies as Lampkin et al. Kraaz et al. simply states that sections of the specimen to be immunostained are mounted on the same multiblock section slide and that several antibodies and an avidin-biotin complex were tested (see middle column of Kraaz et al.). However, Kraaz et al. does not describe how the antibody and avidin-biotin complex testing was performed. Kraaz et al. certainly does not specifically describe comparing and correlating results from "corresponding assigned locations of different substantial copies" as recited in claim 1. Since Kraaz et al. does not describe all the features of claims 1 and 88, the 35 U.S.C. §102(b) rejection over Kraaz et al. must be withdrawn.

Furthermore, dependent claim 6 recites a step of placing an elongated donor specimen in an elongated receptacle of the recipient block. Such placement step does not occur in the method of Kraaz et al. Instead, "[m]ultiblocks containing up to 30 punch specimens from different

tumours or tissues, are made by placing the punched specimens in a warm cast containing a small amount of melted paraffin wax" (middle column). Thus, the punch specimens are placed in a cast with melted paraffin rather than placed in an elongated receptacle already formed in the paraffin block as recited in claim 6.

Enghardt et al.

Claims 1-20, 22, 29-30, 43-44, 49, 53-61, 64-65, 70 and 87-92 have been rejected under 35 U.S.C. §102(b) over Enghardt et al. Similarly to Lampkin et al. and Kraaz et al., Enghardt et al. fails to disclose "comparing the results of the biological analysis in corresponding assigned locations of different substantial copies to determine if there are correlations between the results of the biological analysis at each assigned location" as recited, for example, in claim 1. Enghardt et al. describes performing immunostaining of slides containing sections sliced from the multitissue blocks (see page 53, second column). However, it is not clear what, if any, comparisons were made between test results of different sections of multitissue block obtained according to Enghardt et al. The only specific results that are mentioned are that the "[c]ellular components of the tissues stained according to the manufacturer's specifications for all the antibodies" (see page 54, under the "Results" section). There is no explicit description in Enghardt et al. that results in "corresponding assigned locations of different substantial copies" (claim 1) or "different sections" (claim 16) are compared and correlated as recited in claim 1. Again, any mention of any correlation is conspicuously absent from Enghardt et al. Hence, the pending 35 U.S.C. §102(b) rejection over Enghardt et al. must be withdrawn.

Enghardt et al. also does not specifically disclose "performing a different biological analyses on each copy" (claim 10), or "performing a different biological analysis of each cross-section" (independent claims 16 and 90) and then comparing the results to determine if there are correlations between the different analysis. The only type of analysis that appears be described on page 54 (cited in the Office action) in Enghardt et al. is immunohistochemical assays. The Office action also cites to Table 1, page 52 of Enghardt et al., but this listing of various antibodies does not mean that any correlations were performed between the results for the different antibodies. In addition, since Enghardt et al. only describes one type of biological analysis this reference clearly cannot describe the "parallel analysis" technique recited in claim 16 that includes "comparing a result of each biological analysis in corresponding assigned

locations of difference sections to determine of there are correlations between the results of the different biological analysis."

Moreover, with respect to independent claim 53, Enghardt et al. does not specifically describe "exposing sequential copies" obtained from the multitissue block to a reactive agent. In particular, Enghardt et al.'s relatively vague description of the analytical procedure does not indicate that sequential copies of the multitissue block were analyzed. Hence, the 35 U.S.C. §102(b) rejection of claim 53 (and the claims that depend therefrom) cannot stand.

By way of example, certain dependent claims further distinguish over the disclosure in Enghardt et al. since these claims refer to utilizing clinical characteristics in the analysis of the specimens (see, e.g., claims 9, 12, 14, 59, 60, and 89). Enghardt et al. does not include any mention of such utilization of clinical characteristics. For instance, claim 12 includes "determining whether there are correlations between clinical characteristics, associated with each assigned location, and the different biological analysis." Claim 14 specifies that "the clinical characteristics are determined apart from performing the different biological analysis of each copy of the array; and the characteristics are one or more of patient age, tumor grade, tumor size, node status, and receptor status." The Office action cites to page 55 of Enghardt et al. as disclosing the subject matter of claims 12 and 14, but the closest mention of clinical characteristics is labeling of containers with the "diagnosis." There is no indication in Enghardt et al., though, that such diagnosis is correlated with any biological analysis result.

In addition, claim 22 and new claim 98 state that the substantially cylindrical donor sample core has a diameter of less than 1 mm. The Enghardt et al. method employed a 2 mm diameter punch resulting in a 2 mm diameter sample (see page 51). New claims 99 and 100 each state that the substantially cylindrical sample core has a length of 1 to 4 mm. In contrast, the blocks made according to Enghardt et al. included 9 mm long samples (see page 53).

35 U.S.C. §103 rejections

Claims 21, 45-48 and 93-94

Claims 21, 45-48, and 93-94 have been rejected under 35 U.S.C. §103 over Enghardt et al. The method of dependent claim 21 includes aligning a thin tissue section above the donor block to identify an area of interest from which the donor core sample is taken. Recognizing that

Enghardt et al. does not teach such a step, the Office action on page 14 asserts that "it would have been obvious to one of ordinary skill in the art, having both the donor block and tissue section in close proximity, to align the two, one above the other, for convenient identification."

Applicants first note that the Office action does not cite to any source such as another reference document as providing the requisite motivation for making the asserted modification of Enghardt et al. The Office action notes the advantage of "convenient identification", but this advantage was first recognized by applicants (see page 11, lines 8-35, of the specification) rather than in any prior art cited by the examiner. It is an impermissible use of hindsight to rely upon an advantage first mentioned in the applicants' specification to support an obviousness rejection. If the examiner persists in this rejection, applicants respectfully request that the examiner provide evidence of motivation in the prior art to make the asserted modification to Enghardt et al.

Furthermore, the Office action cites to page 55 of the Enghardt et al. wherein it is stated that "slides and blocks are stored together." However, close proximity during storage simply has no bearing or relation to how the slides and blocks may be used together.

For the foregoing reasons, the obviousness rejection of claim 21 (and dependent claims 93 and 94) must be reconsidered and withdrawn.

With respect to claims 45-48, it is asserted on page 14 of the Office action that "one of ordinary skill in the art would have been motivated to apply the method of Enghardt et al. for claimed used based on tissue being examined and anticipated diagnosis." The Office action again does not provide any evidence such as another prior art document supporting the asserted motivation to use the technique of Enghardt et al. for the purposes recited in claims 45-48. Moreover, Enghardt et al. fails to mention cancer (claim 46), antineoplastic therapy (claim 47) or genetic rearrangement (claim 48) as conditions or tissue that could be the subject of the Enghardt et al. technique. Accordingly, the obviousness rejection of claims 45-48 also must be reconsidered and withdrawn.

Claims 24-29, 31, 50-52, 62-63, 68-69, 71-78 and 86

Claims 24-29, 31, 50-52, 62-63, 68-69, 71-78 and 86 have been rejected under 35 U.S.C. §103 over Enghardt et al. combined with Stapleton et al.

Applicants first reiterate that Stapleton et al. is not entitled to an effective reference date that is prior to the effective priority date of the present application at least with respect to claims

29 and 50-52. As explained in applicants' reply mailed April 4, 2002, claims 29 and 50-52 are entitled to priority of U.S. Provisional Application No. 60/075,979 filed February 25, 1998 (referred to herein as the '979 priority application) (see page 10 of the April 4, 2002 reply). The Stapleton et al. patent issued on August 15, 2000, but claims priority back to a provisional application that was filed on April 14, 1997, which is earlier than the February 25, 1998 filing date of the '979 priority application. Thus, Stapleton et al. is prior art against the present application only to the extent that the Stapleton et al. provisional application satisfies the requirements of a § 102(e) reference. Another copy of the Stapleton et al. provisional application is appended herewith as Exhibit A.

According to MPEP § 2136.03(III), "[t]he 35 U.S.C. 102(e) critical reference date of a U.S. patent . . . . . entitled to the benefit of the filing date of a provisional application under 35 U.S.C. 119(e) is the filing date of the provisional application with certain exceptions **if** the provisional application(s) properly supports the subject matter relied upon to make the rejection in compliance with 35 U.S.C. 112, first paragraph" (emphasis in original). It is submitted that the passages from the Stapleton et al. patent cited in the Office action as evidence of obviousness are not properly supported in the Stapleton et al. provisional application.

In particular, the Stapleton et al. provisional application did not disclose a "parallel analysis" method, and thus there would have been no motivation to combine Stapleton et al. with Enghardt et al. Detecting nucleic acid sequences in a single biological specimen is disclosed in the Stapleton provisional application, but there is no mention of comparing the detected sequences to other sequences from a different biological specimen. The specific passages cited in the Office action (column 6, lines 1-25; column 16, lines 15-18 and Example 7) do not appear, and thus are not supported as required under 35 U.S.C., first paragraph, in the Stapleton et al. provisional application. Accordingly, the pending obviousness rejection of claims 29 and 50-52 must be withdrawn.

With respect to claim 24 (and claims 25-28 that depend therefrom), the Office action relies upon Stapleton et al. as disclosing a nucleic acid array. Upon close inspection, it is apparent that Stapleton et al. does not, in fact, disclose a nucleic acid array. The Stapleton et al. method involves "immobilizing small amounts of cellular or tissue specimens on a matrix for the analysis of nucleic acids" (column 1, lines 22-25). The specimen-impregnated matrix then is contacted with an immobilized sample amplification reaction system (see, e.g., Example 5 of

Stapleton et al.). In sharp contrast, a nucleic acid array is an arrangement of nucleic acids in assigned locations on a matrix (see page 9, lines 16-17, of the present specification). Stapleton et al. does not disclose a matrix that includes an arrangement of previously-identified nucleic acids. Therefore, the asserted combination of Enghardt et al. and Stapleton et al. would not have resulted in the methods of claims 24-28.

It appears that the only mention in Stapleton et al. of any tool even approaching a nucleic acid array is at column 16, lines 14-22. According to this passage, "[i]n order to detect multiple mutations from the same sample [that has been immobilized on a fibrous matrix material], it is possible to use a probe array representing different sequence combinations to which the complementary nucleic acids of the amplified product bind upon diffusing from the immobilized cells." The "probe array" is not described in any more detail in Stapleton et al. This one-sentence vague description from Stapleton et al. certainly does not rise to the level of a sufficient description that clearly teaches a nucleic acid array.

Stapleton et al. also does not describe any further use of the "probe array" other than detecting mutations from a single sample. Applicants, on the other hand, have recognized that nucleic acid arrays can identify a biomarker for use in the biological analysis of claim 1 (i.e., claim 24). More specifically, Stapleton et al. contains no suggestion to use a nucleic acid array to identify a biomarker that could then be used in a different type of biological analysis. The passage in Stapleton et al. (column 5, lines 1-48) cited in the Office action as suggesting combining a nucleic acid array with the technique of Enghardt et al. only describes the advantage of the specific nucleic acid array methodology of Stapleton et al. compared to other nucleic acid array methodologies. This passage contains no hint of using the results obtained by the nucleic acid array to determine the design of a different type of array.

Dependent claim 31 recites a correlation method that involves detecting the overexpression of several specific proteins (vimentin, IGFBP2 and PDGFB). Neither Enghardt et al. nor Stapleton et al. even mention any of these specific proteins.

Claims 62, 63, 68, 69, and 71-78 depend from claim 53. As discussed above in connection with the 35 U.S.C. §102 rejection of claim 53, Enghardt et al. fails to describe or suggest "exposing sequential copies" obtained from the multitissue block to a reactive agent. Stapleton et al. also does not disclose or suggest such sequential exposure. For this reason alone,

the asserted combination of Enghardt et al. and Stapleton et al. does not establish a case of *prima facie* obviousness with respect to claims 62, 63, 68, 69, and 71-78.

Claim 86 depends from claim 1. As discussed above in connection with the 35 U.S.C. §102 rejection of claim 53, Enghardt et al. fails to describe or suggest correlating the results of the biological analysis in corresponding assigned locations of difference substantial copies as recited in claim 1. Stapleton et al. also does not disclose or suggest such correlation. In particular, the array of Stapleton et al. is a fibrous matrix such as that depicted in FIG. 2 of Stapleton et al. There is no suggestion in Stapleton et al. of obtaining substantial copies of the fibrous matrix, unlike the "substantial copies of the recipient array" that are produced according to claim 1. Indeed, Stapleton et al. teaches that the method disclosed therein is superior to methods that involve fixing a specimen in an embedding medium that is then sectioned to obtain analytical samples. It follows that since Stapleton et al. does not suggest making substantial copies the fibrous array, it would not have suggested the correlation technique of claim 1. Thus, claim 86 which depends from claim 1 would not have been *prima facie* obvious.

Claims 32-42

Claims 32-42 have been rejected under 35 U.S.C. §103 over Stapleton et al. combined with An et al. Similar to claim 24, claim 32 calls for the use of a nucleic acid array. As discussed in connection with the obviousness rejection of claim 24, Stapleton et al. does not disclose a nucleic acid array, much less the use of a nucleic acid array as described in claim 32.

An et al. is relied upon to supplying the missing disclosure in Stapleton et al. of using a nucleic acid probe to select a nucleic acid array for screening multiple genes. An et al. discloses nucleic acid probes that can be used for diagnosing diseases. There is no mention in An et al. of nucleic acid arrays meaning that the combination of Stapleton et al. and An et al. would not have suggested any methodology that utilizes nucleic acid arrays. An et al. is also fatally silent with regard to the use of nucleic acid probes to select a nucleic acid array. In summary, there is nothing in either Stapleton et al. or An et al. combined that would have suggested the analysis strategy first envisioned by the applicants as set forth in claim 32.

Claims 66 and 67

Claims 66 and 67 have been rejected under 35 U.S.C. §103 over Enghardt et al. combined with Stapleton et al. and An et al. Claims 66 and 67 depend from claim 53. As discussed above in connection with the 35 U.S.C. §102 rejection of claim 53, Enghardt et al. fails to describe or suggest "exposing sequential copies" obtained from the multitissue block to a reactive agent. Stapleton et al. and An et al. also do not disclose or suggest such sequential exposure. For this reason alone, the asserted combination of Enghardt et al., Stapleton et al. and An et al. does not establish a case of *prima facie* obviousness with respect to claims 66 and 67.

It is respectfully submitted that the present claims are in condition for allowance. Should there be any questions regarding this application, Examiner Forman invited to contact the undersigned attorney at the telephone number shown below.

Respectfully submitted,

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